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Docket No. SHE0081.00

## REMARKS

### **I. Introductory Comments**

In the Final Office Action under reply, the Examiner has removed the objection to the Specification on the basis of incorrect use of trademarks.

The Examiner has maintained the rejections of the claims as follows: under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement (claim 14); under 35 U.S.C. §102(b) as allegedly being anticipated by Minamino et al. (U.S. Patent No. 6,037,452) (claims 1-7, 12-15, 17-22, 24, and 26-30); under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Davis et al. (U.S. Patent No. 4,179,337) (claims 1, 3-4 and 8-10); under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Greenwald (U.S. Patent No. 5,298,643) (claims 1, 3-4 and 8-11); under 35 U.S.C. §103(a) as allegedly being unpatentable over Röstlin et al. [Röstlin et al. (2000) *Bioconjugate Chem.* 11:387-396] in view of Greenwald (U.S. Patent No. 5,298,643) (claims 1, 14 and 16); and under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Longenecker et al. (U.S. Patent No. 4,994,439) (claims 1, 23 and 25).

In addition, the Examiner has added two new claim rejections as follows: under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement (claims 1-15 and 17-30); and under 35 U.S.C. §112, second paragraph, as allegedly raising an issue related to indefiniteness (claims 1-30).

The rejections are traversed for reasons provided below.

### **II. Amendments to the Claims**

Previously, claims 1-30 were pending and claims 31-61 were withdrawn without prejudice. As provided in Section I above, all claims have been amended and new claim 62 has been added.

Support for the changes to the claims is identified below. Additional support other than that identified below may exist in the originally filed application for one or more changes to the claims.

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Claims 1 and 8-11 have been amended to delete (without prejudice) reference to the term "about."

Claim 1 has been amended to recite a conjugate comprising one, two or three water-soluble polymers covalently attached to a Factor VIII moiety. Support for a conjugate comprising one, two or three water-soluble polymers finds support throughout the originally filed specification and claims. See, for example, Paragraphs 0121, 0123 and 0124. The conjunction "or" makes clear that -- with respect to water-soluble polymers -- *only* one, two *or* three water-soluble polymers are covalently attached to the Factor VIII moiety. In addition, the previously added phrase "wherein at least about 82% of conjugates in the composition" has been deleted; originally filed claim 1 supports subject matter not reciting this claim element.

Claims 2-18 and claims 26-30 have been amended to recite a "conjugate" in view of the amendment to claim 1 to provide correct antecedent basis.

Claim 14 has been amended to delete (without prejudice) reference to "deletion variants, substitution variants or addition variants."

The dependencies of claims 19-25 have been amended in view of new claim 62.

New claim 62 has been added to introduce the concept of "compositions" of the previously claimed conjugates. Compositions of conjugates are provided in the first sentence of Paragraph 0121.

As support for the changes is found in the application as filed, no new matter is introduced by the entry of the above-identified changes. The changes to the claims are made for clarification purposes only should not be interpreted as acquiescence in any claim rejection.

### III. The Interview of June 28, 2005

At the undersigned's request, an interview with the Examiner was conducted on June 28, 2005. During the interview, the propriety of one or more rejections was discussed (although no resolution was reached), as discussed in more detail below.

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#### IV. The Restriction Requirement

Applicant continues to reserve its right to petition the Commissioner to review the requirement for restriction, deferring the filing of such petition until after final action on or allowance of the claims, but not later than appeal. See 37 C.F.R. §1.144.

#### V. The Original Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner maintained the rejection of claim 14 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner has taken this position in view of claim 14's recitation of the phrase "deletion variants, substitution variants or addition variants of any of the foregoing."

As the phrase "deletion variants, substitution variants or addition variants of any of the foregoing" has been removed (without prejudice) from the claim, reconsideration and removal of the rejection under 35 U.S.C. §112, first paragraph, are respectfully requested.

#### VI. The Rejection Under 35 U.S.C. §102(b)

The Examiner maintained the rejection of claims 1-7, 12-15, 17-22, 24, and 26-30 under 35 U.S.C. §102(b) as allegedly being anticipated by Minamino et al. (U.S. Patent No. 6,037,452). Ostensibly, the Examiner has taken the position that each and every element of the rejected claims can be found in Minamino et al.

The rejection is respectfully traversed in view of the following remarks.

The standard for anticipation was provided in Applicant's previous response.

Among other things to support maintenance of the anticipation rejection in the Final Office Action, the Examiner alleged certain deficiencies with respect to added language in the independent claims. Applicant has rendered moot these alleged deficiencies by removing (without prejudice) the added language by way of the present Amendment.

The Examiner also tried to support maintenance of the anticipation rejection in the Final Office Action by emphasizing Minamino et al.'s teaching that Factor VIII conjugates "containing polyalkylene glycol added to about 50-70% of amino groups in molecules may be structurally useful." The present claims, however, distinguish over such highly substituted species (given the number of amino groups in Factor VIII and Factor VIIIa) inasmuch as the claims are directed to conjugates comprising one, two or three water-soluble polymers covalently attached to a Factor

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VIII moiety, wherein each water-soluble polymer has a nominal average molecular weight in the range of greater than 5,000 Daltons to 150,000 Daltons.

The Examiner also points to Minamino et al.'s teaching of varying pH and concentration with the aim of providing various degrees of substitution. Whether Minamino et al. teaches the ability to provide various degrees of substitution, however, is irrelevant to the question of whether Minamino et al. discloses each and every element of the rejected claims. As Minamino et al. simply does not disclose conjugates comprising one, two or three water-soluble polymers covalently attached to a Factor VIII moiety, wherein each water-soluble polymer has a nominal average molecular weight in the range of greater than 5,000 Daltons to 150,000 Daltons, the anticipation rejection cannot stand. Reconsideration and removal of the rejection under 35 U.S.C. 102(b) for at least the reasons provided above are respectfully requested.

#### VII. The First Rejection Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 1, 3-4 and 8-10 under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Davis et al. (U.S. Patent No. 4,179,337).

The rejection is respectfully traversed in view of the following remarks.

The standard for establishing a *prima facie* case of obviousness was provided in Applicant's previous response.

In the Final Office Action, the Examiner relied on the arguments provided with respect to maintaining the anticipation rejection in order to support maintenance of this obviousness rejection. Applicant has shown in the above Section VI, however, that the pending claims are distinguishable over Minamino et al.

In addition, as previously pointed out by Applicant, Davis et al. does not cure the deficiencies of Minamino et al. As previously pointed out by Applicant, Davis et al. describes utilization of "between 10 and 100, suitably between 15 to 50 moles of polymer per mole of polypeptide." See Davis et al. at column 3, lines 10-13. Further, Davis et al. describes compositions comprising between 10 and 100 polymer moieties per molecule of insulin (Davis et al., claim 5) and enzyme (Davis et al., claim 19). Clearly, Davis et al. does not describe conjugates comprising one, two or three water-soluble polymers covalently attached to a Factor

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VIII moiety, wherein each water-soluble polymer has a nominal average molecular weight in the range of greater than 5,000 Daltons to 150,000 Daltons.

Consequently, as neither Minamino et al. nor Davis et al. teaches or suggests all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 3-4 and 8-10 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above are respectfully requested.

### VIII. The Second Rejection Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 1, 3-4 and 8-11 under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Greenwald (U.S. Patent No. 6,037,452).

The rejection is respectfully traversed in view of the following remarks.

The standard for establishing a *prima facie* case of obviousness was provided in Applicant's previous response.

In the Final Office Action, the Examiner relied on the arguments provided with respect to maintaining the anticipation rejection in order to support maintenance of this obviousness rejection. Applicant has shown in the above Section VI, however, that the pending claims are distinguishable over Minamino et al.

In addition, as previously pointed out by Applicant, Greenwald describes reacting aryl imidate activated polyalkylene oxide with  $\epsilon$ -NH<sub>2</sub> moieties of lysines and that "the degree of conjugation is limited only by the number of  $\epsilon$ -NH<sub>2</sub> moieties of lysines." See Greenwald at column 8, lines 4-15. Again, given the 158 amine-containing lysine residues in native Factor VIII (see Applicant's specification at paragraph [0107]) it is clear that Greenwald describes compositions of conjugates wherein each conjugate has a relatively large number of polymers attached to a protein or polypeptide. Thus, Greenwald neither discloses nor suggests conjugates comprising one, two or three water-soluble polymers covalently attached to a Factor VIII moiety, wherein each water-soluble polymer has a nominal average molecular weight in the range of greater than 5,000 Daltons to 150,000 Daltons.

Consequently, as neither Minamino et al. nor Greenwald teaches or suggests all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the

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obviousness rejection of claims 1, 3-4 and 8-11 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above are respectfully requested.

**IX. The Third Rejection Under 35 U.S.C. §103(a)**

The Examiner has maintained the rejection of claims 1, 14 and 16 under 35 U.S.C. §103(a) as allegedly being unpatentable over Röstin et al. [Röstin et al. (2000) *Bioconjugate Chem.* 11:387-396] in view of Greenwald (U.S. Patent No. 6,037,452).

The rejection is respectfully traversed in view of the following remarks.

The standard for establishing a *prima facie* case of obviousness was provided in Applicant's previous response.

In the Final Office Action, the Examiner relied on the arguments provided with respect to maintaining the anticipation rejection in order to support maintenance of this obviousness rejection. Applicant has shown in the above Section VI, however, that the pending claims are distinguishable over Minamino et al.

In addition, as previously pointed out by Applicant, Röstin et al. describes the preparation of several compositions of conjugates. Each of Röstin et al.'s described compositions of conjugates is prepared using polymers having molecular weights of 3,000 Daltons or 5,000 Daltons. Thus, Röstin et al. neither discloses nor suggests conjugates comprising one, two or three water-soluble polymers covalently attached to a Factor VIII moiety, wherein each water-soluble polymer has a nominal average molecular weight in the range of greater than 5,000 Daltons to 150,000 Daltons.

Consequently, as neither Röstin et al. nor Greenwald teach or suggest all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 14 and 16 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above are respectfully requested.

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**X. The Fourth Rejection Under 35 U.S.C. §103(a)**

The Examiner has maintained the rejection of claims 1, 23 and 25 under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Longenecker et al. (U.S. Patent No. 4,994,439).

The rejection is respectfully traversed in view of the following remarks.

The standard for establishing a *prima facie* case of obviousness was provided in Applicant's previous response.

In the Final Office Action, the Examiner relied on the arguments provided with respect to maintaining the anticipation rejection in order to support maintenance of this obviousness rejection. Applicant has shown in the above Section VI, however, that the pending claims are distinguishable over Minamino et al.

In addition, as previously pointed out by Applicant, Longenecker et al. is completely silent with respect to compositions containing any conjugates.

Thus, as neither Minamino et al. nor Longenecker et al. teaches or suggests all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 23 and 25 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above are respectfully requested.

**XI. The Second Rejection Under 35 U.S.C. §112, First Paragraph**

The Examiner rejected claims 1-15 and 17-30 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner has taken this position in view of claim 1's recitation of the phrase "wherein at least about 82% of the conjugates in the composition each has one to three water-soluble polymers covalently attached to a Factor VIII moiety."

As this phrase has been removed (without prejudice) from claim 1, reconsideration and removal of the rejection under 35 U.S.C. §112, first paragraph, are respectfully requested.

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## **XII. The Rejection Under 35 U.S.C. §112, Second Paragraph**

The Examiner rejected claims 1-30 under 35 U.S.C. §112, second paragraph, as allegedly raising an issue related to indefiniteness. Specifically, the Examiner has taken this position in view of claim 1's recitation of the phrase "at least about."

As the phrase this phrase has been removed (without prejudice) from claim 1, reconsideration and removal of the rejection under 35 U.S.C. §112, first paragraph, are respectfully requested.

## **XIII. Conclusion**

In view of the foregoing, Applicant submits that the pending claims satisfy the requirements of patentability and are therefore in condition for allowance. Reconsideration and withdrawal of all rejections are respectfully requested and a prompt mailing of a Notice of Allowance is earnestly solicited.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 500348.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 620-5506.

Respectfully submitted,  
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